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A Triple Layer Matrix Tablet Of Aceclofenac As Biphasic Release

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Abstract: ***The objective of the present study was to develop biphasic release tablets of Aceclofenac by wet granulation using Hydroxy propyl methyl cellulose K -100 and K15 for sustained release and lactose and Microcrystalline cellulose for immediate release. The drug excipient mixtures were subjected to preformulation studies. The tablets were subjected to physicochemical studies, invitro drug release, kinetic studies and stability studies. The physicochemical properties of tablets were found within the limits. Aceclofenac is a non steroidal anti-inflammatory agent used in symptomatic treatment of rheumatoid arthritis, osteoarthritis and spondylitis. The drug release from optimized formulations was extended for a period of 12 hrs. The kinetic treatment of selected formulation (F7M7) showed that the release of drug follows Hixon crowell models. The optimized formulations were subjected to stability studies for one month at 45° temperature with RH 75±5% and showed there were no significant changes in drug content, physicochemical parameters and release pattern. Based on the results of the in vitro studies, it was concluded that the Aceclofenac matrix tablets provided biphasic release.***

Keywords: ***Aceclofenac, Matrix tablets, Sustained release, immediate release Wet granulation, Hydroxy Propyl Methyl Cellulose K -100, K-15, Lactose, Microcrystalline cellulose.***

I. INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are considered to be the first-line drugs in the symptomatic treatment of rheumatoid arthritis, osteoarthritis and spondylitis, Aceclofenac is one of them1. It is a newer derivative of Diclofenac with low gastrointestinal complications. The short biological half-life (3- 4h) and dosing frequency more than one per day make Aceclofenac an ideal candidate for sustained release. To reduce the frequency of administration and to improve patient compliance, a once-daily sustained release formulation of Aceclofenac is desirable. Matrix tablets composed of drug and polymer as release retarding material offer the simplest approach in designing a sustained release system. The present study aims to develop sustained release matrix tablets using hydrophilic matrix materials2, such as HPMC- K 15 and HPMC- K 100 along with drug in varying proportions by wet granulation method. And for immediate release lactose and Microcrystalline cellulose along with drug by wet granulation method. Matrix tablets were prepared by either wet granulation or direct compression method. Currently available sustained matrix tablets are generally prepared by wet granulation method. The aim of the present work was to prepare biphasic release matrix tablets of Aceclofenac and to study the effect of *invitro* release characteristics, kinetics of the prepared formulations and stability studies.

II. MATERIALS AND METHOD

MATERIALS: Aceclofenac was proceured from IPCA Pharmaceuticals, Mumbai, Microcrystalline cellulose from Research lab. Fine chem., Mumbai, HPMC K15 M from signet Chemicals, HPMC K 100 M from signet chemicals, PVP K30 from signet chemicals, Aerosil from signet chemicals, Ethyl cellulose from signet chemicals, Lactose DC from Research lab. Fine chem. Industry Mumbai, Magnesium

stearate from Pure chem. Lab. Hyderabad, Croscarmellose sodium from signet lab.

METHOD

ULTRAVIOLET -VISIBLE SPECTROSCOPY

Determination of λmax in Methanol, 0.1 N HCL, Phosphate buffer 7.5.

The UV spectrum of Aceclofenac was obtained using UV Jasco V630.Accurately weighed 10 mg of the drug was dissolved in sufficient quantity of Methanol, 0.1 N Hydrochloric acid, Phosphate buffer pH 6.8, Distilled Water & 0.1N Sodium hydroxide and volume made up to 10 ml. The stock solution was diluted to obtain a concentration of 100 µg/ml. 1 ml of aliquot was withdrawn and volume was made upto 10 ml using respective solvent to obtain the concentration of 10 µg/ml. The resultant solution was scanned from 400 to 200 nm and the spectrum was recorded to obtain the value of maximum Wavelength in respective solvents.

Preparation of Calibration curve in Methanol, 0.1 N HCL, and Phosphate buffer 7.5.

Stock solution of drug 100µg/ml was prepared in different solvents like Methanol, 0.1 N HCL, Phosphate buffer pH 7.5, Distilled Water & 0.1N NaOH. The stock solution of 100µg/ml was used to prepare different dilutions in respective solvents. The absorbance of resulting solutions were measured using respective blank solvents by UV-visible spectrophotometer.

INFRA-RED SPECTRUM

The infrared absorption spectrums of Aceclofenac were recorded with the wave number 1800-600 cm^{-1} by using Fourier transform infrared spectrophotometer (Bruker).

FORMULATION OF ACECLOFENAC IMMEDIATE LAYER

Different polymers were employed in order to formulate the immediate layer. The excipient was to be selected on basis of marketed innovator. Different polymer in ratio of on basis of aqueous formulation, non aqueous and dry granulation process. (i.e. water, Isopropyl alcohol).

Ingredients	**A1**	**A2**	**A3**
Aceclofenac	75	75	75
Lactose	20	25	15
MCC	25	20	25
PVP K30	5	5	5
Water	q.s	q.s	q.s
Croscarmellose sodium	10	10	5
Aerosil	5	5	5
Talc	5	5	5
	145	**145**	**145**

Table 1: Formulation with aqueous Granulation

Ingredients	**A4**	**A5**	**A6**
Aceclofenac	75	75	75
Lactose	25	30	15
MCC	15	15	15
PVP K30	5	5	5
Isopropyl alcohol	q.s	q.s	q.s
Croscarmellose sodium	10	10	15
Aerosil	5	5	5
Talc	5	5	5
	145	**145**	**145**

Table 2: Formulation with aqueous Non Aqueous Granulation

Ingredients	**A7**	**A8**	**A9**
Aceclofenac	75	75	75
Lactose	30	10	25
MCC	10	30	10
PVP K30	5	5	5
Croscarmellose sodium	5	5	15
Aerosil	5	5	10
Talc	5	5	5
	145	**145**	**145**

(All quantities are in mg).

Table 3: Formulation with Direct Granulation

EVALUATION OF ACECLOFENAC IMMEDIATE LAYER WITH DIFFERENT MEDIUM

Tablets prepared of Aceclofenac as immediate layer was evaluated for Hardness, Thickness, Friability, Uniformity of weight, Drug content (Assay) and Dissolution test.

HARDNESS TEST

Although hardness test is not an official test, tablet should have sufficient handling qualities during packing and transportation. Hardness of tablet was measured using Monsanto hardness tester. It is the pressure required to fracture diametrically placed tablets by applying force. The hardness of randomly selected 6 tablets, from each batch was determined and mean hardness was taken into account, which was expressed in kg/cm^2.

THICKNESS

All tablets were subjected for thickness measurement by using digital vernier caliper. All the measurements were made in triplicate.

FRIABILITY TEST

For the friability test sample of 20 whole tablets were selected randomly. All tablets were dedusted carefully and weighing accurately the required number of tablets were placed in the drum and rotated about 100 times. Tablets were removed from the drum and loose dust was removed from the tablets, weighed accurately. The percentage weight loss should not be more than 1% of the total weight.

UNIFORMITY OF WEIGHT

20 units were selected at random and were weighed individually, and average weightwas calculated. Not more than 2 of the individual weight of tablets should deviate from the average weight by more than 5%.

DRUG CONTENT (ASSAY)

Weigh and powder 20 tablets. Weigh accurately a quantity of the powder containing about 10 mg of Aceclofenac, add 50 ml of 0.1 M sodium hydroxide, shake for 20 minutes and dilute to 100.0 ml with 0.1 M sodium hydroxide. Mix, filter, dilute 5.0 ml of the filtrate to 100.0 ml with water and measure the absorbance of the resulting solution at the maximum at about 275 nm. Calculate the content of Aceclofenac taking 520 as the specific absorbance at 275 nm. The tablet preparation complies with the test, only if each individual content lies between 97.5 to 101.5 % of the average content.

SELECTION OF COMPOSITION

From the evaluation parameter the non aqueous medium is to be selected as it complies with all post compression parameter. Factorial design for non aqueous formulation.

Variables	Factor
Independent	
X1	Lactose
X2	MCC
Dependent	
Y1	% CDR
Y2	Drug content

Translation of the Coded Levels in Actual Units

Coded levels	Actual value in mg	
	X1	X2
-1	10	15
0	20	20
+1	30	25

3^2Full Factorial Design Layouts

Sr. No.	Formulation Code	Coded Factor Levels with Combination	
		X1(mg)	X2(mg)
1	F1	10	15
2	F2	20	15
3	F3	30	15
4	F4	10	20
5	F5	20	20
6	F6	30	20
7	F7	10	25
8	F8	20	25
9	F9	30	25

Table 4: Variables in optimization batch

Ingredients	F1	F2	F3
Aceclofenac	75	75	75
Lactose	10	20	30
MCC	15	15	15
PVP K30	5	5	5
Isopropyl alcohol	q.s	q.s	q.s
Croscarmellose sodium	30	20	10
Aerosil	5	5	5
Talc	5	5	5
	145	**145**	**145**

Ingredients	F4	F5	F6
Aceclofenac	75	75	75
Lactose	10	20	30
MCC	20	20	20
PVP K30	5	5	5
Isopropyl alcohol	q.s	q.s	q.s
Croscarmellose sodium	25	15	5
Aerosil	5	5	5
Talc	5	5	5
	145	**145**	**145**

Ingredients	F7	F8	F9
Aceclofenac	75	75	75
Lactose	10	20	30
MCC	25	25	25
PVP K30	5	5	5
Isopropyl alcohol	q.s	q.s	q.s
Croscarmellose sodium	20	10	-
Aerosil	5	5	5
Talc	5	5	5
	145	**145**	**145**

Table 5: Composition of immediate layer with non aqueous Granulation (isopropyl alcohol)

MANUFACTURING PROCESS OF ACECLOFENAC IMMEDIATE LAYER

STEP1: Aceclofenac, MCC DC and lactose of different ratios were weighed accurately and mixed in geometric proportion and sifted through 40# mesh.

STEP 2: PVP K30 were mix in IPA and tartrazine were a weighed accurately and mix.

STEP 3: Croscarmellose sodium, talc, and Aerosil were weighed and mix and sifted through 40#.

STEP 4: Formulation was made with wet granulation method .

STEP 5: Mix all step 1,2,3 throughly and compress in 8mm of punch.

EVALUATION OF ACECLOFENAC IMMEDIATE LAYER WITH NON AQUEOUS MEDIUM

Tablets prepared of aceclofenac as immediate layer was evaluated for Hardness, Thickness, Friability, Uniformity of weight, Drug content (Assay)and Dissolution test.

✓ *HARDNESS TEST*

Hardness of tablet was measured using Monsanto hardness tester. It is the pressure required to fracture diametrically placed tablets by applying force. The hardness of randomly selected 6 tablets, from each batch was determined and mean hardness was taken into account, which was expressed in kg/cm^2.

✓ *THICKNESS*

All tablets were subjected for thickness measurement by using digital vernier caliper. All the measurements were made in triplicate.

✓ *FRIABILITY TEST*

For the friability test sample of 20 whole tablets were selected randomly. All tablets were dedusted carefully and weighing accurately the required number of tablets were placed in the drum and rotated about 100 times. Tablets were removed from the drum and loose dust was removed from the tablets, weighed accurately. The percentage weight loss should not be more than 1% of the total weight.

✓ *UNIFORMITY OF WEIGHT*

20 units were selected at random and were weighed individually, and average weightwas calculated. Not more than 2 of the individual weight of tablets should deviate from the average weight by more than 5%.

✓ *DRUG CONTENT(ASSAY)*

An accurately weighed quantity of tablet powder equivalent to about 25 mg of Aceclofenac (on labeled claim basis) was transferred to 50 mL volumetric flask, containing methanol, sonicated for 15 min and diluted up to the mark with methanol to get the concentration 500 µg/mL (Stock solution). The solution was then filtered through Whatmann filter paper (no. 41). A 5.0 mL portion of stock solution was diluted to 50 mL with methanol to give a solution of 50µg/mL. Aliquots of this solution were appropriately diluted to get concentration of 15µg/mL of ACF (on label claim basis). The absorbance of the resultant solution were read at the selected wavelengths and the amount of ACF was estimated by comparison with the standard and by taking A(1%,1cm) as 324.47±0.61 at 277.2 nm (Method I) and comparing the derivative absorbance of standard with that of the sample at 261.6 nm (Method II). The results of estimation are shown in Table II .

✓ *DISSOLUTION TEST*

The test is designed to determine compliance with the dissolution requirement for solid dosage forms administered orally.

Apparatus: 2 (Paddle)
Medium: 900 ml of pH 7.5 phosphate buffer.
Speed: 50 rpm.
Times: 45 min.
Temperature: 37^{0}c.

Tablet was placed in jar containing 900ml of pH 7.5 phosphate buffer for 45min. and samples at different time interval 10ml of aliquots were removed and filtered through whatman filter paper no.52 at time specified time interval and analyzed by UV-Visible spectroscopy at 273nm using pH 7.5 phosphate buffer as blank. Tolerance: the percentages of the labeled amount of Aceclofenac dissolved at the times specified.

FORMULATION AND EVALUATION OF ACECLOFENAC SUSTAINED LAYER

FORMULATION OF ACECLOFENAC SUSTAINED LAYER

Polymers were to be selected on basis of marketed innovator, polymers as hypermellose K15M, Hypermellose K 100M, Microcrystalline cellulose, are to be taken in ratio. The blend was prepare using those retarding excipients to form a sustained layer. The tablet was compressed using 12 mm punch at a weight of 483 mg. The drug release was estimated.

Variables	Factor
Independent	
X1	HPMC K15
X2	HPMC K100
Dependent	
Y1	% CDR
Y2	Drug content

Translation of the Coded Levels in Actual Units

3^{2}Full Factorial Design Layouts

Sr. No.	Formulation Code	Coded Factor Levels with Combination	
		X1(mg)	X2(mg)
1	M1	40	30
2	M2	45	30
3	M3	50	30
4	M4	40	35
5	M5	45	35
6	M6	50	35
7	M7	40	40
8	M8	45	40
9	M9	50	40

Table 6: Variables in optimization batch

Ingredients	Aceclofenac HPMC K15: HPMC K100: MCC			
	M1	M2	M3	M4
Barrier layer				
Hypermellose K15 m	40	45	50	40
MCC	70	65	60	65
HPMC K 100 M	30	30	30	35
Sustained layer				
Aceclofenac	225	225	225	225
HPMC K 15 M	40	45	50	40
HPMC K100 M	30	30	30	35
Ethyl cellolose	10	10	10	10

MCC	30	25	20	25
PVP K 30	8	8	8	8
Aerosil	5	5	5	5
Magnesium state	5	5	5	5
Total	493	493	493	493

Ingredients	Aceclofenac + barrier layer	
	M5	M6
Barrier layer		
Hypermellose K15 m	45	50
MCC	70	55
HPMC K 100 M	35	35
Sustained layer		
Aceclofenac	225	225
HPMC K 15 M	45	50
HPMC K100 M	35	35
Ethyl cellolose	10	10
MCC	20	15
PVP K 30	8	8
Aerosil	5	5
Magnesium state	5	5
Total	493	493

(All quantities are in mg)

Ingredients	Aceclofenac + barrier layer		
	M7	M8	M9
Barrier layer			
Hypermellose K15 m	40	45	50
MCC	60	55	50
HPMC K 100 M	40	40	40
Sustained layer			
Aceclofenac	225	225	225
HPMC K 15 M	40	45	50
HPMC K100 M	40	40	40
Ethyl cellolose	10	10	10
MCC	20	15	10
PVP K30	8	8	8
Aerosil	5	5	5
Magnesium stearate	5	5	5
Total	493	493	493

(All quantities are in mg)

Table No.7 Composition of various Aceclofenac barrier and sustained layer

MANUFACTURING PROCESS

a. ACECLOFENAC SUSTAINED LAYER

- ✓ *STEP1:* MCC DC, ethylcellulose, HPMC K15, HPMC K100 were weighed accurately and mixed in proportion and sifted through 40# mesh.
- ✓ *STEP 2:* Aceclofenac were weighed accurately and mixed in geometric proportion with step 1 mixture and sifted through 40# mesh.
- ✓ *STEP 3:* Aerosil and magnesium stearate were weighed accurately and mixed and sifted through 60# mesh.
- ✓ *STEP 4:* Mix both the mixtures of step 1 and step 3.
- ✓ *STEP 5:* compress the powder in 12mm of punch.

b. BARRIER LAYER

- ✓ *STEP1:* Hypermellose K15M, HPMC K100 were weighed accurately.
- ✓ *STEP 2:* MCC DC were weighed accurately and mixed in geometric proportion and sifted through 40# mesh. .
- ✓ *STEP 3:* Mix both the mixtures of step 1 and step 2.

The accurately weighed powders of both layers were then subjected to direct compression to form a bilayer tablet using 12mm punch on Rotary tablet minipress-I (Rimek, Karnavati Engineering Ltd., Mehsana, Gujarat).

EVALUATION OF ACECLOFENAC AND BARRIER SUSTAINED LAYER

Sustained release Tablets were prepared. These tablets were evaluated for Hardness, Thickness, Friability, Uniformity of weight, Drug content (Assay), Disintegration test and Dissolution test.

✓ *HARDNESS TEST*

Hardness of tablet was measured using Monsanto hardness tester. It is the pressure required to fracture diametrically placed tablets by applying force. The hardness of randomly selected 6 tablets, from each batch was determined and mean hardness was taken into account, which was expressed in kg/cm^2.

✓ *THICKNESS*

All tablets were subjected for thickness measurement by using digital vernier caliper. All the measurements were made in triplicate.

✓ *FRIABILITY TEST*

For the friability test sample of 20 whole tablets were selected randomly. All tablets were dedusted carefully and weighing accurately the required number of tablets were placed in the drum and rotated about 100 times. Tablets were removed from the drum and loose dust was removed from the tablets, weighed accurately. The percentage weight loss should not be more than 1% of the total weight.

✓ *UNIFORMITY OF WEIGHT*

20 units were selected at random and were weighed individually, and average weight was calculated. Not more than 2 of the individual weight of tablets should deviate from the average weight by more than 5%.

✓ *DISINTEGRATION TEST*

Disintegration test determines whether dosage forms such as tablets disintegrates within prescribed time when placed in a liquid medium under prescribed experimental conditions. Disintegration is defined as that state in which no residue of the unit under test remains on the screen of the apparatus or, if a residue remains, it consist of fragment of disintegrated parts of tablet component part such as insoluble coating of the tablets is soft mass with no palpable core.

✓ *DRUG CONTENT (ASSAY)*

An accurately weighed quantity of tablet powder equivalent to about 25 mg of Aceclofenac (on labeled claim basis) was transferred to 50 mL volumetric flask, containing methanol, sonicated for 15 min and diluted up to the mark with methanol to get the concentration 500 µg/mL (Stock solution). The solution was then filtered through Whatmann filter paper (no. 41). A 5.0 mL portion of stock solution was diluted to 50 mL with methanol to give a solution of 50µg/mL. Aliquots of this solution were appropriately diluted to get concentration of 15µg/mL of ACF (on label claim basis). The absorbance of the resultant solution were read at the selected wavelengths and the amount of ACF was estimated by comparison with the standard and by taking A(1%,1cm) as 324.47±0.61 at 277.2 nm (Method I) and comparing the derivative absorbance of standard with that of the sample at 261.6 nm (Method II). The results of estimation are shown in Table II.

✓ *DISSOLUTION TEST*

The test is designed to determine compliance with the dissolution requirement for solid dosage forms administered orally.

Apparatus: Paddle
Medium: 900 ml of 7.5 phosphate buffer.
Speed and time: 100 rpm and 12 hours
Temperature: 37^0c.

Tablet was placed in jar containing 900ml of 7.5 phosphate buffer for 12 hours and samples at different time interval 10ml of aliquots were removed and filtered through whatman filter paper no.52 at time at specific time interval and analyzed by UV-Visible spectroscopy at 275nm using 6.8 phosphate buffer as a blank. D. Not less than 90% of the stated amount of Aceclofenac.

Ingredients **Formulation of immediate layer**	**F3**
Aceclofenac	75
Lactose	30
MCC	15
PVP K30	5
Isopropyl alcohol	q.s
Croscarmellose sodium	10
Aerosil	5
Talc	5
Total	**145**

Ingredients **Formulation of sustained layer**	**M7**
Barrier layer	
Hypermellose K15 m	40
MCC	60
HPMC K 100 M	40
Sustained layer	
Aceclofenac	225
HPMC K 15 M	40
HPMC K100 M	40
Ethyl cellolose	10
MCC	20
PVP K 30	8
Aerosil	5
Magnesium state	5
Total	493

Table 8: formulation of optimize batch of Immediate and Sustained layer

METHOD OF PREPARATION OF OPTIMIZED TRILAYER TABLET

✓ The sustained and barrier layer of weight 493 mg powder was half Compressed with lower compression force using 12mm of circular concave punch on Rotary tablet minipress-I (Rimek, Karnavati Engineering Ltd., Mehsana, Gujarat).
✓ Over this compress layer the immediate layer of weight 145mg of batch. Was placed and compress to form a trilayer tablet.

EVALUATION OF OPTIMIZED BATCH OF IMMEDIATE AND SUSTAINED LAYER

✓ *HARDNESS*

Hardness of tablet was measured using Monsanto hardness tester. It is the pressure required to fracture diametrically placed tablets by applying force. The hardness of randomly selected 6 tablets, from each batch was determined and mean hardness was taken into account, which was expressed in kg/cm^2.

✓ *THICKNESS*

All tablets were subjected for thickness measurement by using digital vernier caliper. All the measurements were made in triplicate.

✓ *FRIABILITY*

Friability is the measure of tablet strength. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm for 4 minutes, dropping the tablets to a distance of 6 inches in each revolution.

Method

For the friability test sample of 10 whole tablets were selected randomly. All tablets were dedusted carefully and weighing accurately the required number of tablets were placed in the drum and rotated about 100 times. Tablets were removed from the drum and loose dust was removed from the tablets, weighed accurately. The percentage weight loss should not be more than 1% of the total weight.

$$\text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

✓ *UNIFORMITY OF WEIGHT*

20 units were selected at random and were weighed individually, and average weight was calculated. Not more than 2 of the individual weight of tablets should deviate from the average weight by more than 5%.

Sr. No.	Average weight of tablet	% deviation allowed
1.	80 mg or less	10
2.	More than 80 mg but less that 250 mg	7.5
3.	250 mg or more	5

Table 9: Specifications for tablets as per Indian Pharmacopoeia

✓ *DISINTEGRATION TIME OF ACECLOFENAC TRIPLE LAYER*

The disintegration time for Aceclofenac layer of tablet was measured using the disintegrtion test appratus for tablets as described in the Pharmacopoeia. Six Tablets were placed in the disintegration tubes of disintegration appratus (Electrolab) and time required for complete disintegration without leaving any residues on the screen was recorded as disintegration time.

✓ *IN VITRO DRUG RELEASE OF OPTIMIZED TRILAYER TABLET*

Dissolution study of Aceclofenac sustained layer

The test is designed to determine compliance with the dissolution requirement for solid dosage forms administered orally.

Apparatus: 2 (Paddle)
Medium: 900 ml of pH 7.5 phosphate buffer.
Speed: 100rpm.
Times: 1, 4, 8, and 12 hours.
Temperature: 37^0c.

Tablet was placed in jar containing 900ml of pH 7.5 phosphate buffer for 12 hours and samples at different time interval 10ml of aliquots were removed and filtered through whatmann filter paper no.52 at time interval specified (1, 4, 8, and 12 hours.) and analyzed by UV-Visible spectroscopy by using simultaneous estimation method at 273 using pH 7.5 phosphate buffer as blank.

FORMULATION OF REPRODUCIBLE BATCH OF TRILAYER TABLET

To check the reproducibility of the batch, reproducible batch of Trilayer tablet was prepared with the same formula and procedure as that of optimized bilayer tablet. The drug release of reproducibility batch was checked for similarity to that of optimized batch and marketed formulation. Composition of reproducible batch.

Ingredients Formulation of immediate layer	F3
Aceclofenac	75
Lactose	30
MCC	15
PVP K30	5
Isopropyl alcohol	q.s
Croscarmellose sodium	10
Aerosil	5
Talc	5
Total	**145**

Ingredients Formulation of sustained layer	M7
Barrier layer	
Hypermellose K15 m	40
MCC	60
HPMC K 100 M	40
Sustained layer	
Aceclofenac	225
HPMC K 15 M	40
HPMC K100 M	40
Ethyl cellolose	10
MCC	20
PVP K 30	8
Aerosil	5
Magnesium state	5
Total	493

Table 10: Formulation of reproducible batch of Trilayer tablet of Aceclofenac

EVALUATION OF PREPARED BLEND MIXTURES OF BOTH LAYERS

✓ *BULK DENSITY*

The bulk density was obtained by dividing the mass of powder by the bulk volume. The sample equivalent to 10 g was accurately weighed and filled in a 100 mL graduated cylinder and the powder was leveled and the unsettled volume, (V_0) was noted. The bulk density was calculated by the formula

$$\text{Bulk density } (\rho_0) = \frac{M}{V_0}$$

Where, ρ_0 = Bulk density,
M = Mass of powder taken and
V_0 = Apparent unsettled volume.

✓ *TAPPED DENSITY*

The tapped density was determined by mechanically tapping the measuring cylinder or by using the digital bulk density tester and the tapped volume was noted. The tapped density was calculated by the formula

$$Tapped\ density\ (\rho_0) = \frac{M}{V_t}$$

Where, ρ_t = tapped density,
M = weight of powder and
V_t= tapped volume of powder in cm^3.

✓ *HAUSNER'S RATIO*

Hausner ratio gives an idea regarding the flow of the blend. It is the ratio of tapped density to the apparent density. Hausners ratio was calculated as

$$Hausnerratio = \frac{Bulk}{Tapped}$$

Sr. No.	Hausners Ratio	Flow property
1	1 – 1.11	Excellent
2	1.12 - 1.18	Good
3	1.26 – 1.34	Poor

Table 11: Relationship between Hausner ratio and flow property

✓ *COMPRESSIBILITY INDEX*

The compressibility index measures of the propensity of powder to be compressed. The packing ability of drug was evaluated from change in volume, which is due to rearrangement of packing occurring during tapping (USP, 2006). It is indicated as carrs compressibility index (CI) and can be calculated as follows:

Sr. No.	% Compressibility	Flow property
1	5-15	Excellent
2	12-16	Good
3	18-21	Fairly acceptable
4	23-35	Poor
5	33-38	Very poor
6	< 40	Extremely poor

Table 12: Relationship between % compressibility and flow property

✓ *ANGLE OF REPOSE*

FUNNEL METHOD: Funnel with a sound stem of 20 to 30 mm diameter was attached to the burette stand the height of which was adjusted such that its tip just touches the apex of powder. The graph paper sheet was placed below the funnel. The powder was allowed to flow through the funnel freely onto the surface of the graph paper sheet. Circle was marked around the heap covering approximately 90% of total powder bed. Procedure was repeated thrice to obtain the average reading & average diameter.

Sr. No.	Flow character	Angle of Repose(0^0)
1	Excellent	25-30
2	Good	31-35
3	Fair	36-40
5	Passable	41-45
6	Poor	46-55
7	Very poor	56-65
8	Very, very poor	>66

Table 13: Relationship between angle of repose (θ) and flow

EVALUATION OF PREPARED TRILAYER TABLET

✓ *HARDNESS*

Hardness of tablet was measured using Monsanto hardness tester. It is the pressure required to fracture diametrically placed tablets by applying force. The hardness of randomly selected 6 tablets, from each batch was determined and mean hardness was taken into account, which was expressed in kg/cm^2.

✓ *THICKNESS*

All tablets were subjected for thickness measurement by using digital vernier caliper. All the measurements were made in triplicate.

✓ *FRIABILITY*

Friability is the measure of tablet strength. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm for 4 minutes, dropping the tablets to a distance of 6 inches in each revolution.

METHOD

For the friability test sample of 10 whole tablets were selected randomly. All tablets were dedusted carefully and weighing accurately the required number of tablets were placed in the drum and rotated about 100 times. Tablets were removed from the drum and loose dust was removed from the tablets, weighed accurately. The percentage weight loss should not be more than 1% of the total weight.

✓ *UNIFORMITY OF WEIGHT*

20 units were selected at random and were weighed individually, and average weightwas calculated. Not more than 2 of the individual weight of tablets should deviate from the average weight by more than 5%.

Sr. No	Average weight of tablet	%deviation allowed
1.	80 mg or less	10
2.	More than 80 mg but less that 250 mg	7.5
3.	250 mg or mor	5

Table 14: Specifications for tablets as per Indian Pharmacopoeia – 2007

✓ *DISINTEGRATION TIME OF ACECLOFENAC LAYER*

The disintegration time for Aceclofenac layer of tablet was measured using the disintegrtion test appratus for tablets as described in the Pharmacopoeia. Six Tablets were placed in the disintegration tubes of disintegration appratus (Electrolab) and time required for complete disintegration without leaving any residues on the screen was recorded as disintegration time.

✓ *DRUG CONTENT (ASSAY)*

An accurately weighed quantity of tablet powder equivalent to about 25 mg of Aceclofenac (on labeled claim basis) was transferred to 50 mL volumetric flask, containing methanol, sonicated for 15 min and diluted up to the mark with methanol to get the concentration 500 µg/mL (Stock solution). The solution was then filtered through Whatmann filter paper (no. 41). A 5.0 mL portion of stock solution was diluted to 50 mL with methanol to give a solution of 50µg/mL. Aliquots of this solution were appropriately diluted to get concentration of 15µg/mL of ACF (on label claim basis). The absorbance of the resultant solution were read at the selected wavelengths and the amount of ACF was estimated by comparison with the standard and by taking A(1%,1cm) as 324.47±0.61 at 277.2 nm (Method I) and comparing the derivative absorbance of standard with that of the sample at 261.6 nm (Method II). The results of estimation are shown in Table II.

✓ *IN VITRO DISSOLUTION STUDIES OF ACECLOFENAC TABLET*

DISSOLUTION STUDY OF ACECLOFENAC SUSTAINED LAYER

The test is designed to determine compliance with the dissolution requirement for solid dosage forms administered orally.

Apparatus: 2 (Paddle)
Medium: 900 ml of pH 7.5 phosphate buffer.
Speed: 50 rpm.
Times: 1, 4, 8, an12 hours.
Temperature: 37^0c.

Tablet was placed in jar containing 900ml of pH 7.5 phosphate buffer for 20 hours and samples at different time interval 10ml of aliquots were removed and filtered through whatmann filter paper no.52 at time interval specified (1, 4, 8, 12 and 20 hours.) and analyzed by UV-Visible spectroscopy by using simultaneous estimation method at 273 nm using pH 7.5 phosphate buffer as blank.

DISSOLUTION KINETIC STUDY

Various mathematical models like; Zero-order model, First-order model, Higuchi (Matrix) model and Korsmeyer-Peppas Model were evaluated with respect to the dissolution profiles of the optimized formulations. PCP disso software was used to fit models to dissolution profiles.

STABILITY STUDIES

Stability study of optimized trilayer tablet formulation was carried out to point out any visual physical or chemical changes made in the formulation after storing it at elevated temperature and humidity conditions. Chemical and physical stability of reproducible trilayer tablet formulation was assessed at 40±2 ^{0}c/ 75±5% RH as per ICH Guidelines in the stability chamber tempo instrument pvt.ltd. TI-710. Tablets equivalent to 75mg of immediate Aceclofenac layer and 225mg of sustained Aceclofenac layer were filled and were with packed with aluminium strips and stored for 3 months. Samples were analyzed at 0, 30, 60, & 90 days for physical appearance, drug content, disintegration time and in-vitro dissolution profile.

III. RESULTS AND DISCUSSION

UV-VISIBLE SPECTROSCOPY OF ACECLOFENAC

IN 0.1N HYDROCHLORIC ACID (HCL)

Solution of Aceclofenac was prepared in 0.1N hydrochloric acid and scanned between 400-200nm using UV spectrophotometer showed peak at wavelength 275nm. However, keeping in mind the probable concentration likely to be encountered while carrying out In- vitro release studies and considering the predicted theoretical λ_{max} involved, the working λ_{max} was decided as 275 nm as shown in figure no.1.

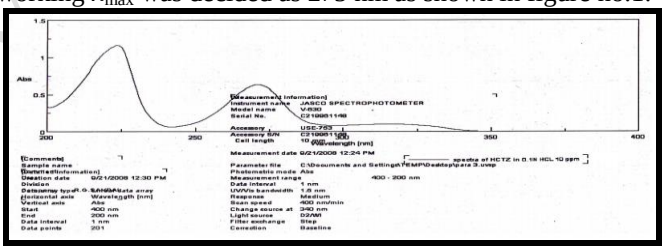


Figure 1: UV-Visible spectrum of Aceclofenac in 0.1 N Hydrochloric Acid (HCl)

PREPARATION OF CALIBRATION CURVE

IN 0.1N HYDROCHLORIC ACID (HCL)

Calibration curve of Hydrochlorothiazide was performed in 0.1N Hydrochloric acid as Hydrochlorothiazide is soluble in 0.1N Hydrochloric acid. 0.1N Hydrochloric acid solution of drug was very clear and readily analyzed by UV spectrophotometer. The calibration curve was found to be linear in the concentration range of 4-20µg/ml. Having coefficient of regression value R^2 =0.998 and Slope y = 0.070x - 0.023.The calibration curve of Hydrochlorothiazide in 0.1N Hydrochloric acid.

Sr. No.	Concentration (ppm)	Absorbance at 276 nm
1.	10	0.585
2.	12	0.699
3.	14	0.815
4.	16	0.930

5.	18	1.057
6.	20	1.169

Table 15: Absorbance's of Aceclofenac in 0.1 N Hydrochloric acid (HCl) at 275nm

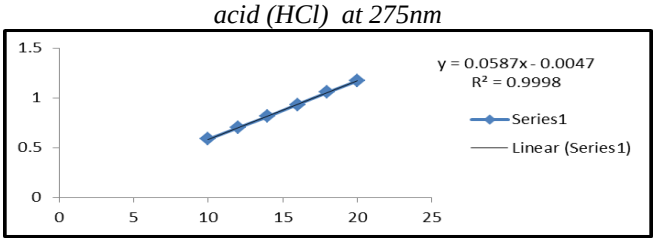


Figure 2: Calibration curve of Aceclofenac in 0.1 N Hydrochloric Acid (HCl) at 275 nm

IN METHANOL

Calibration curve of Aceclofenac was performed in Methanol as Aceclofenac is soluble in Methanol. This solution drug was very clear and readily analyzed by UV spectrophotometer. The calibration was found to be linear in the concentration range of 5-25 µg/ml. Having coefficient of regression value R^2 = 0.998 and slope y=0.006 X +0.024. The calibration curve of Aceclofenac in Methanol shown in figure no.3

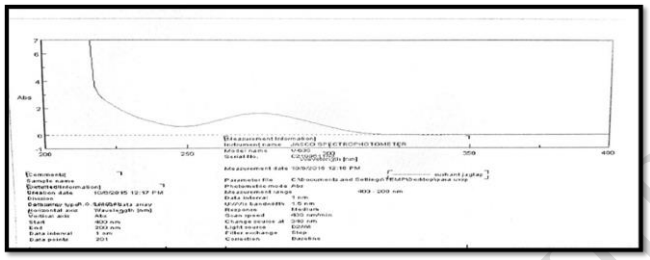


Figure 3: spectrum of Aceclofenac in methanol at 257 nm

IN METHANOL

Calibration curve of Hydrochlorothiazide was performed in Methanol as Hydrochlorothiazide is soluble in Methanol. Methanol solution of drug was very clear and readily analyzed by UV spectrophotometer. The calibration curve was found to be linear in the concentration range of 4-12µg/ml. Having coefficient of regression value R² = 0.986 and Slope y = 0035x+0.084.

Sr. No.	Concentration (ppm)	Absorbance at 275 nm
1.	5	0.2656
2.	10	0.4515
3.	15	0.5998
4.	20	0.7369
5.	25	0.9990

Table 16: Absorbance's of Aceclofenac in methanol at 275nm

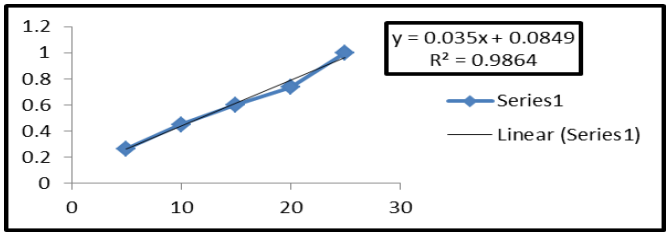


Figure 4: Calibration curve of Aceclofenac in Methanol at 275 nm

IN PHOSPHATE BUFFER PH 7.5

Solutions of Aceclofenac was prepared in phosphate buffer pH 7.5 and scanned between 400-200 nm using UV spectrophotometer showed peak at wavelength 273 nm. However, keeping in mind the probable concentrations likely to be encountered while carrying out In-vitro release studies and considering the predicted theoretical λ_{max} involved, the working λ_{max} was decided as 275 nm as shown in figure no.5

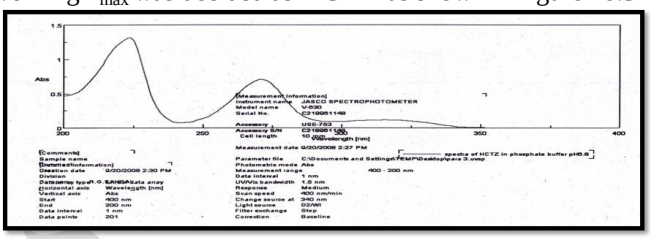


Figure 5: Spectrum of Aceclofenac in phosphate buffer pH 7.5

IN PHOSPHATE BUFFER PH 7.5

Calibration curve of Aceclofenac was performed in phosphate buffer ph7.5 Phosphate buffer pH 7.5 solution of drug was very clear and readily analyzed by UV spectrophotometer. The calibration curve was found to be linear in the concentration range of 4-12µg/ml. Having coefficient of regression value R^2 =0.998 and Slope y = 0.070x + 0.014.

Sr. No.	Concentration (ppm)	Absorbance at 257 nm
1.	4	0.2924
2.	6	0.4348
3.	8	0.5880
4.	10	0.7027
5.	12	0.8595

Table 17: Absorbance's of Aceclofenac in phosphate buffer pH 7.5 at 273nm

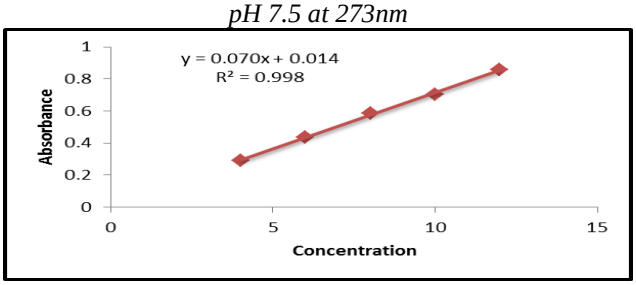


Figure 6: Calibration curve of Aceclofenac in phosphate buffer pH 7.5 at 273 nm

INFRA-RED SPECTRUM

Infra-red spectrum of Aceclofenac is shown in figure no.7 The major peaks observed and corresponding functional groups are given table no.17. Infra- red spectrum shows peak characteristic of structure of Aceclofenac.

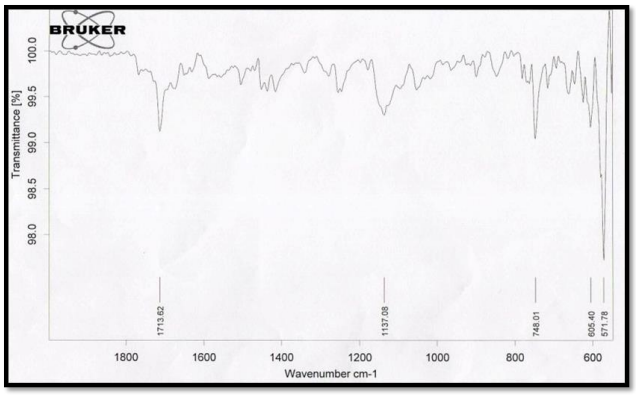


Figure 7: FTIR spectrum of Aceclofenac

Sr. No.	Functional group	Standard frequency (cm-1)	Observed frequency (cm-1)
1.	C-Br (stretch)	680-500	571
2.	C-H (bend)	600-700	748
3.	C-H	730-770	748
4.	C-O (stretch)	1070-1550	1137
5.	C=O (stretch)	1710-1720	1713

Table 18: Major Peaks observed in IR spectrum of Aceclofenac

The absorption bands shown by Aceclofenac are characteristics of the groups present in its molecular structure. The presence of absorption bands corresponding to the functional groups present in the structure of Aceclofenac confirms the identification and purity of gifted Aceclofenac sample.

EVALUATION OF POWDER BULK FOR IMMEDIATE LAYER TABLETS

Formulation code	Angle of repose(θ°) Mean± S.D	Bulk density (gm/cm^3) Mean± S.D	Tapped density (gm/cm^3) Mean± S.D	Compressibility index (%) Mean± S.D	Hausner's ratio Mean± S.D
A1	27.83±1.87	0.3488±0.003	0.4054±0.004	13.92±1.70	1.16±0.023
A2	29.62±2.43	0.3432±0.005	0.4065±0.003	15.5±0.513	1.18±0.026
A3	32.28±0.9295	0.3281±0.002	0.3722±0.004	11.82±0.68	1.13±0.008
A4	30.75±1.811	0.3333±0.002	0.3806±0.003	12.43±0.97	1.14±0.012
A5	31.22±0.7700	0.3409±0.003	0.4043±0.0066	14.14±0.796	1.18±0.016
A6	30.49±1.0966	0.3481±0.006	0.4054±0.004	11.92±0.733	1.16±0.010
A7	29.98±0.4156	0.3370±0.001	0.3926±0.001	15.42±1.013	1.16±0.0085
A8	32.01±0.8050	0.3355±0.0045	0.3742±0.010	13.23±0.181	1.11±0.043
A9	30.57±1.057	0.3575±0.007	0.4025±0.007	11.27±0.72	1.15±0.015

Table 19: Evaluation of Powder Bulk for immediate layer with different Formulation (i.e Aqueous, non aqueous, dry granulation)

EVALUATION OF IMMEDIATE RELEASE LAYER

The tablets were formulated as per stated in

All the prepared tablet formulations were subjected to compendia test for post compression evaluation such as friability, hardness, thickness, uniformity of weight and content uniformity results obtained for the same are given in table no.20. All tablets were found in the given in official compendia for the test such as friability, uniformity of weight, and drug content.

Formulation Code	Average Weight (mg) Mean ± S.D	Weight variation %	Hardness (kg/cm^2) Mean± S.D	Thickness (mm) Mean± S.D	Friability (%) Mean ± S.D	Drug content (%) Mean± S.D	Disintegration time (min)
A1	142±0.5021	0.0207	3.51±0.015	2.18±0.005	0.92±0.016	97.8±0.614	1.52
A2	141.1±0.4818	0.2075	3.21±0.015	3.12±0.0057	0.97±0.012	98.5±0.782	1.50
A3	140.1±0.227	0.0878	3.32±0.049	3.08±0.0057	0.93±0.012	98.7±0.974	1.50

Table 20: Evaluation of different composition immediate layer (with aqueous medium)

As the aqueous medium contain water in formulation the disintegration time does not complies , it disintegrate in less time. So the aqueous solvent is not suitable for immediate layer.

Formulation Code	Average Weight (mg) Mean ± S.D	Weight variation %	Hardness (kg/cm^2) Mean± S.D	Thickness (mm) Mean± S.D	Friability (%) Mean± S.D	Drug content (%) Mean± S.D	Disintegration time (min)
A4	142±0.5021	0.0207	3.51±0.015	3.18±0.005	0.92±0.016	97.8±0.614	3.52
A5	141.1±0.4818	0.2075	3.21±0.015	3.12±0.005	0.97±0.012	98.5±0.782	3.62
A6	140.1±0.227	0.0878	3.32±0.049	3.08±0.0057	0.93±0.012	98.7±0.974	3.77

Table 21: Evaluation of different composition immediate layer (with non- aqueous)

In the non aqueous medium the all post compression test complies. So wet granulation process for immediate layer is done by using Isopropyl alcohol as non aqueous solvent.

Formulation Code	Average Weight (mg) Mean ± S.D	Weight variation %	Hardness (kg/cm^2) Mean± S.D	Thickness (mm) Mean± S.D	Friability (%) Mean± S.D	Drug content (%) Mean± S.D	Disintegration time
A7	120±0.5021	0.0207	3.51±0.015	2.18±0.005	0.92±0.016	95.8±0.614	2.22
A8	125.1±0.4818	0.2075	3.21±0.015	2.12±0.0057	0.97±0.012	92.5±0.782	2.27
A9	122.1±0.227	0.0878	3.32±0.049	3.08±0.0057	0.93±0.012	90.7±0.974	2.78

Table 22: Evaluation of different composition immediate layer (with Dry granulation)

Dry medium shows the change in average weight of each tablet, and its affect on flow property of powder. So is not complies to formulate immediate layer of Aceclofenac.

Formulation Code	Average Weight (mg) Mean ± S.D	Weight variation %	Hardness (kg/cm^2) Mean± S.D	Thickness (mm) Mean± S.D	Friability (%) Mean± S.D	Drug content (%) Mean± S.D	Disintegration time (min)
F1	145±0.5021	0.2058	3.51±0.015	3.18±0.005	0.98±0.015	98.2±0.614	3.52
F2	143.7±0.488	0.0852	3.21±0.015	3.12±0.0057	0.97±0.010	98.8±0.782	2.25

F3	145.1±0.258	0.0878	3.32±0.049	3.08±0.0057	0.85±0.012	98.5±0.974	3.75
F4	142.7±0.288	0.3577	3.41±0.01	3.91±0.0057	0.82±0.015	98±1.170	2.75
F5	147.5±0.587	0.4575	3.63±0.015	3.95±0.020	0.89±0.020	97.8±0.538	2.57
F6	142.3±0.587	0.0878	4.15±0.005	3.94±0.027	0.92±0.016	98.5±0.815	2.20
F7	145.8±0.207	0.0275	4.28±0.005	2.52±0.087	0.92±0.012	98.9±0.678	2.27
F8	142.7±0.287	0.0285	3.87±0.02	2.99±0.0098	0.87±0.111	98.6±0.763	3.22
F9	142.7±0.557	0.1088	3.64±0.208	3.58±0.0028	0.89±0.008	98.1±0.517	3.52

Table 23: Evaluation of immediate layer with non aqueous medium

IN VITRO STUDIES OF IMMEDIATE LAYER

Comparative studies of drug with marketed formulation are done. This shows the drug range in limit in 45 min.

Time (min)	% drug release F1	F2	F3	F4	F5	F6	F7	F8 F9	Limit
5	22.33	15.25	20.95	11.65	23.25	10.78	25.65	15.25	22.52	10-25%
10	38.36	28.25	25.75	20.27	42.65	28.77	42.58	20.28	25.75	30-40%
15	43.04	40.28	25.32	38.25	48.98	32.57	48.58	35.25	32.75	40-45%
20	51.63	47.98	38.25	38.52	57.32	48.57	59.38	42.58	48.75	50-55%
25	60.42	60.75	58.35	48.78	68.25	57.75	69.75	55.25	48.25	60-65%
30	68.24	62.57	60.32	55.32	68.57	62.28	80.32	57.52	58.28	70-75%
35	80.65	75.28	75.27	65.32	78.95	78.35	88.87	68.75	72.57	80-85%
40	87.17	82.78	78.88	78.98	80.25	80.97	92.32	75.87	82.57	85-90%
45	89.62	90.85	91.74	88.52	88.41	89.85	90.41	87.45	89.41	NLT 90%

From the above in vitro studies the F3 batch of immediate layer was found to be complies with the limit. It is further taken for formulation of trilayer tablet

EVALUATION OF POWDER BULK FOR SUSTAINED AND BARRIER LAYER TABLETS

Formulation code	**Angle of repose(0°) Mean± S.D**	**Bulk density (gm/cm^3) Mean± S.D**	**Tapped density (gm/cm^3) Mean± S.D**	**Compressibility index (%) Mean± S.D**	**Hausner's ratio Mean± S.D**
M1	27.78±1.85	0.3788±0.003	0.4052±0.004	13.95±1.70	1.18±0.023
M2	28.78±1.43	0.3432±0.005	0.4065±0.003	15.5±0.513	1.19±0.026
M3	33.25±0.9295	0.3281±0.002	0.3722±0.004	11.82±0.68	1.13±0.008
M4	30.75±1.811	0.3333±0.002	0.3806±0.003	12.43±0.97	1.14±0.012
M5	31.25±0.7700	0.3412±0.003	0.4045±0.0066	14.15±0.796	1.19±0.016
M6	30.49±1.0966	0.3481±0.006	0.4054±0.004	11.92±0.733	1.16±0.010
M7	32.98±0.285	0.3370±0.001	0.3926±0.001	15.42±1.013	1.16±0.0085
M8	32.01±0.8050	0.3355±0.0045	0.3742±0.010	13.23±0.181	1.11±0.043
M9	30.49±1.304	0.3401±0.0023	0.4021±0.0047	12.65±0.1001	1.18±0.014

Table 24: Evaluation of Powder Bulk for sustained and barrier Tablets

EVALUATION OF SUSTAINED AND BARRIER LAYER TABLET

The tablets were formulated as per stated in

All the prepared tablet formulations were subjected to compendia test for post compression evaluation such as friability, hardness, thickness, uniformity of weight and content uniformity results obtained for the same are given in table no.22. All tablets were found in the given in official compendia for the test such as friability, uniformity of weight, and drug content.

Formulation Code	**Average Weight (mg) Mean ± S.D**	**Weight variation %**	**Hardness (kg/cm^2) Mean ± S.D**	**Thickness (mm) Mean± S.D**	**Friability (%) Mean± S.D**	**Drug content (%) Mean± S.D**	**Disintegration time (min)**
M1	482±0.8027	0.0357	4.51±0.015	4.07±0.005	0.92±0.016	90.52±0.614	30.25
M2	481.8±0.4818	0.6701	4.21±0.015	4.12±0.057	0.97±0.012	92.62±0.782	28.87
M3	482.5±0.4333	0.0357	4.40±0.049	4.08±0.057	0.93±0.012	92.62±0.897	32.27
M4	480.2±0.585	0.6928	4.41±0.01	3.91±0.057	0.85±0.016	96.85±1.170	30.57
M5	480.7±0.522	0,6642	3.58±0.015	3.95±0.020	0.89±0.020	92.84±0.538	30.22
M6	487.8±0.5972	0.0007	4.21±0.005	3.94±0.057	0.92±0.016	91.85±0.815	28.27
M7	490.7±0.3306	0.0357	4.72±0.005	4.10±0.072	0.81±0.012	98.33±0.678	28.22
M8	483.7±0.5587	0.0714	4.27±0.02	4.11±0.057	0.96±0.012	97.55±0.763	27.77
M9	485.7±0.8055	0.3928	3.94±0.01	0.89±0.008	90.41±0.51	97.28±0.85	30.77

Table 25: Evaluation of Aceclofenac sustained and barrier layer

IN-VITRO DRUG RELEASE OF ACECLOFENAC SUSTAINED TABLET

Dissolution studies of Aceclofenac tablet from each other determined by UV method. The best batch of Aceclofenac tablet was selected on the basis of in vitro drug release to prepare tablet. In vitro dissolution study of the formulation containing polymer in different concentration were compared. The results of dissolution studies are tabulated no.23

Time	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**Marketed limit**
30	3.909	3.909	4.65	3.25	4.25	2.62	3.90	4.90	3.27	0-5%
45	4.364	5.364	5.87	5.364	4.98	4.25	5.36	5.36	5.364	1-5%
60	4.411	5.25	5.32	5.58	5.25	5.41	6.25	5.411	5.411	1-5%
120	5.60	8.60	7.87	8.15	8.60	8.98	7.98	8.60	8.60	1-10%
180	11.85	15.52	7.85	15.85	11.57	10.85	15.85	15.85	15.85	10-15%
240	19.21	20.98	22.22	22.21	22.21	21.58	23.25	21.21	18.21	15-20%
300	17.76	28.76	18.98	27.76	27.76	26.78	26.25	27.76	27.76	25-30%
360	15.36	28.65	25.36	35.36	30.87	35.75	32.78	35.36	35.36	30-35%
420	28.78	33.78	38.25	38.78	32.78	38.78	37.37	35.78	33.78	35-40%
480	37.94	30.20	47.94	38.25	47.65	45.25	47.94	47.94	45.94	45-50%
540	44.99	42.32	55.10	52.57	55.25	52.98	54.99	56.98	54.99	50-55%
600	46.44	42.10	55.47	50.75	56.44	55.25	56.44	56.37	56.44	55-60%
660	69.47	61.15	62.47	62.37	68.27	65.27	67.47	65.47	65.38	60-80%
720	97.62	98.36	95.33	98.25	98.6	98.12	99.41	97.85	96.34	NLT 85%

Table 26: In-Vitro drug release of Aceclofenac sustained layer

From the above in-vitro studies of Aceclofenac sustained layer M7 batch complies with the marketed formulation.

EVALUATION OF OPTIMIZED BATCH OF IMMEDIATE AND SUSTAINED LAYER

The various batches was to be made of Aceclofenac trilayer in combination with the immediate layer and the sustained layer. The post compression evaluation such as friability, hardness, thickness, uniformity of weight, disintegration time & content uniformity results. Evaluation optimized batch is given in table no.27

Formulation Code	**Average Weight (mg) Mean ± S.D**	**Weight variation %**	**Hardness (kg/cm^2) Mean± S.D**	**Thickness (mm) Mean± S.D**	**Friability (%) Mean± S.D**	**Drug content (%) Mean± S.D**	**Disintegration time (min)**
F3M7	640±0.2027	0.02872	4.85±0.027	5.10±0.005	0.97±0.015	98.8±0.57	28.75

Table 27 Evaluation of optimized batch of Immediate and sustained layer

IN-VITRO DRUG RELEASE OF OPTIMIZED BATCH F3M7OF TRILAYER TABLET

The prepared trilayer tablets were subjected to dissolution test to assess in-vitro release of Aceclofenac immediate layer and Aceclofenac sustained layer from the optimized trilayer tablet as compared to specifications given in official compendia. Dissolution rate of trilayer tablets are given in table.no.28.

Time	% drug release	Limits
15	15.78	5-15%
30	18.75	15-20%
45	25.25	20-25%
60	28.57	25-30%
240	40.75	35-40%
360	52.28	45-55%
480	72.98	65-75%
600	85.82	80-90%
720	97.87	NLT 95%

Table 28: dissolution comparision of F3M7

EVALUATION OF REPRODUCIBLE BATCH OF TRILAYER TABLET OF ACECLOFENAC

EVALUATION OF PRECOMPRESSION PARAMETERS

The blends of both layer of reproducible batch were subjected for measurement of bulk density, tapped density, Hausner's ratio and Carr's index..From the results of Compressibility (Carr's) index and Hausner's ratio it can be clearly concluded that the Metoprolol Succinate and Hydrochlorothiazide tablet blend were having excellent flow properties, fair to good compressibility which allow these formulation mixtures to be directly compressed into tablets and good flow of the mixture from hopper with good content uniformity in final tablets. As per USP/NF angle of repose value between 25-30^{0}and below indicates excellent flow properties of the both blends i.e. less or no interparticulate friction or resistance to movement between particles.

Sr.No.	Precompression parameters	Aceclofenac IR blend F3	Aceclofena cSR blend M7
1	Bulk density (gm/ml)	0.752	0.7153
2	Tapped density (gm/ml)	0.7857	0.8782
3	Compressibility index %	15.636	18.46
4	Hausner's ratio	0.722	0.7282
5	Angle of repose	20.72	22.57

Table 29: Results of precompression evaluation of formulation mixture

EVALUATION OF POST COMPRESSION PARAMETERS

All the prepared bilayer tablets were subjected to compendial test for post compression evaluation such as friability, hardness, thickness, uniformity of weight, disintegration time & content uniformity results. Evaluation reproducible batch is given in table no.29.

Sr. No.	Parameter	Limits	Observation
1	Weight variation	635.7-724.5mg (±5%)	Complies
2	Thickness	6.5±0.5mm	5.15±0.02
3	Hardness	NLT 4 Kg/cm^2	4.27±0.027
4	Friability	NMT 1%	0.97
6	Drug content of Aceclofenac	92.5-107.5% of label claim	98.77
7	Disintegration Time of Aceclofenac	NMT 30 Min	28.57

Table 30: Evaluation of reproducible batch of Trilayer Tablet

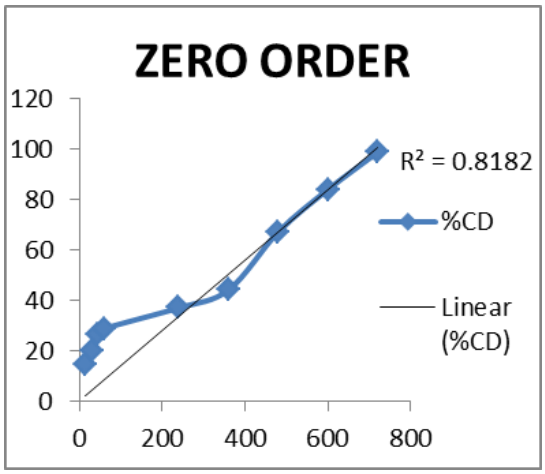
IN-VITRO STUDIES OF OPTIMIZED BATCH OF ACECLOFENAC

Time	% drug release	Limits
	Reproducible batch	
15	15.78	5-15%
30	18.75	15-20%
45	25.25	20-25%
60	28.57	25-30%
240	40.75	35-40%
360	52.28	45-55%
480	72.98	65-75%
600	85.82	80-90%
720	97.87	NLT 95%

Table 31: In vitro studies of Aceclofenac triple layer tablet

DISSOLUTION KINETIC STUDY

To analyze the mechanism of drug release from the tablet, data obtained from the drug release studies was subjected to different mathematical models (Zero order, First order, Matrix (Higuchi) and Korsmeyer's Peppas). The correlation coefficient (r^2) was used as an indicator for the best fitting for each of the models. Table no.31 and table no.32 shows the Kinetics treatment for the optimized formulations. Different mathematical models for drug release mechanism of Aceclofenac.



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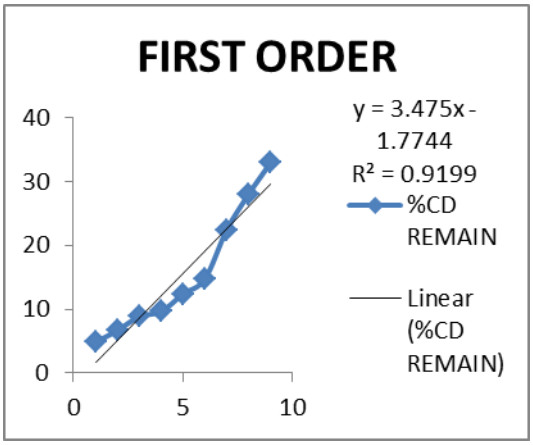

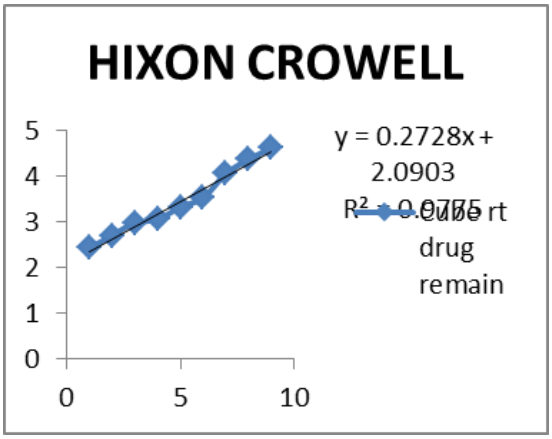

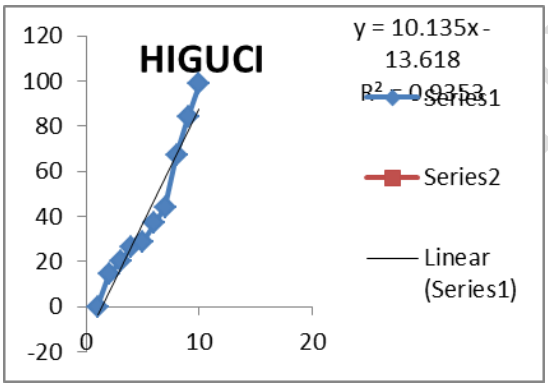

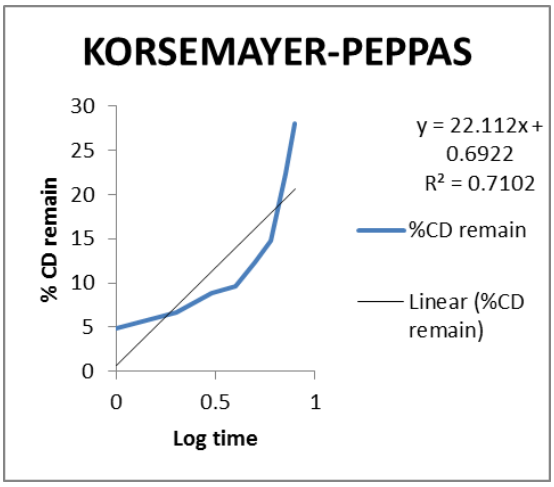

Figure 8: Dissolution study

Code	Zero order	1st order	Hixon crowell	Peppas	
				R^2	n-Value
F8	0.818	0.919	0.977	0.710	0.692

Table 32: The best fitting model (Average)

Code	Model fitting	R^2 value
F8	Hixon Crowell	0.977

Table 33: Drug release kinetics for optimized batch

DISCUSSION: From the R^2 value it was concluded that the drug release profile of reproducible batch of Aceclofenac followed Hixon crowell order release pattern.

SIMILARITY FACTOR (F_2) STUDY

FDA and the European Agency for the Evaluation of Medicinal Product, suggest that two dissolution profiles are declared similar if f_2 is between 50 and 100.

$f_2$values for reproducible trilayer tablet formulation was determined using excel and it was shown in table no. 34

Sr.No	Formulation	f_2 value
1.	F3M7	75

Table 34: f_2 value for reproducible Trilayer Tablet formulation

As per FDA guideline F7M7 formulations can be considered as showing similardissolution profile as that of reference products. Based on above observations it can be concluded that formulations F7M7 the most suitable formulations among the all the formulations as it show similar dissolution profile as that of marketed formulations. Hence, it was further considered for stability study.

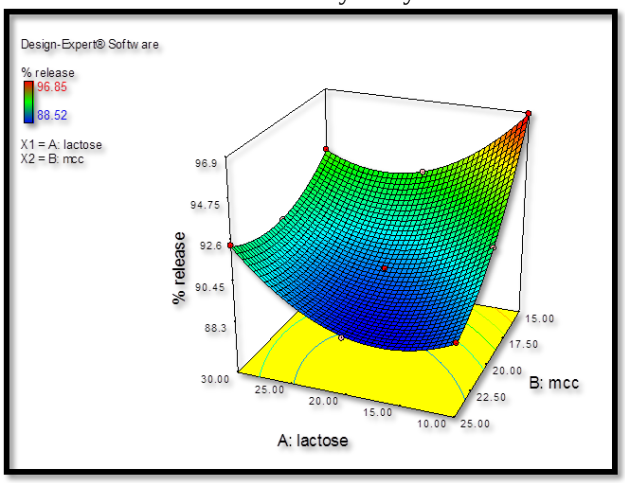

Figure 9: Plot for % release immediate release tablet

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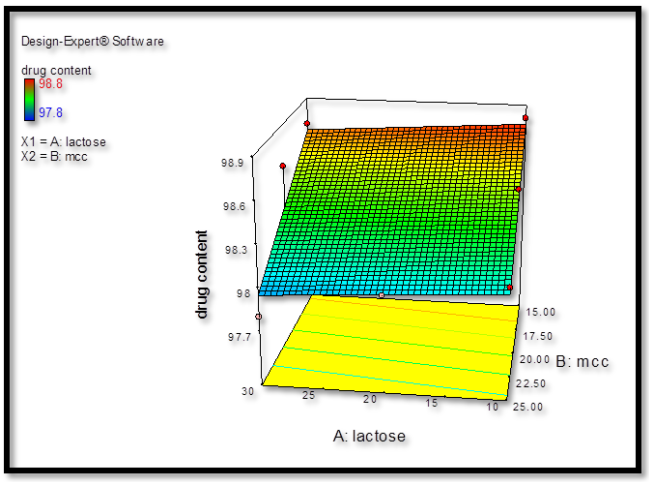

Figure 10: Plot of drug content of immediate release tablet

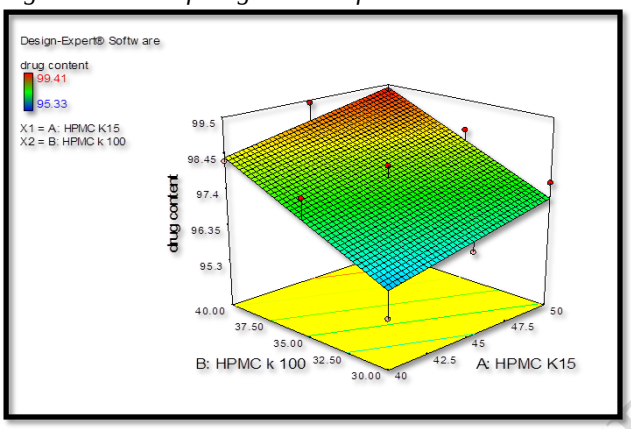

Figure 11: Plot of drug content for sustained release tablet

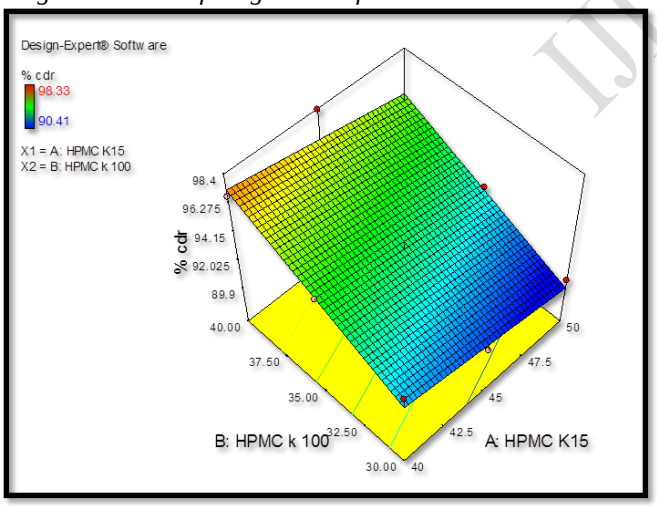

Figure 12: Plot of % release for sustained release tablet

STABILITY STUDIES

Optimized formulations of trilayer tablet were subjected to stability studies as per ICH guidelines. Various parameters such as Physical appearance, drug content, disintegration time and in vitro dissolution profile release were measured before and after 30, 60 and 90 days of stability. Results of stability studies are shown in table no.33.Physical appearances of all formulations were unaffected or did not show any significant changes.

Stability parameter at 40±2 ^{0}C/ 75±5% RH	**Time (Days)**		
	0	**30**	**60**
Aceclofenac Trilayer tablet			
1) Disintegration (Min.)	22.48	28.33	30.25
2) Drug content %	97.86	95.79	97.66
3) In vitro dissolution	88.82	89.01	90.88

Table 35: Stability studies of optimized formulations

Results of stability studies showed that there is no significant change in above mentioned parameters after elevated temperature and humidity conditions during stability studies. Thus it can be proved from the stability studies that the prepared formulation is stable and not much affected by elevated humidity and temperature conditions.

IV. CONCLUSION

Above studies successfully demonstrated the use Hydroxypropyl methyl cellulose K15 M and use Hydroxypropyl methyl cellulose K100M as carrier for formation of Aceclofenac Sustained releases layer and Microcrystalline cellulose, lactose, croscarmellose in formation of Aceclofenac immediate layer. Combination of HPMC K15M, HPMC K100M excipients were effectively sustain the release of Aceclofenac up to 12 hours and show the drug release as per specification given in USP. From the FT-IR and DSC characterization it can be concluded that the Aceclofenac was compatible with the polymers used in formulation of matrix tablet.

The final trilayer tablet was formulated using optimized batch of Aceclofenac immediate; ayer and Aceclofenac sustained layer i.e. F7 and M7respectively which shows better drug release when compared with market product. No significant change was observed in physical appearance, drug content and in vitro drug release before and after stability studies for 3 months.Hence, it is finally concluded that, the trilayer tablet technology can be successfully applied for sustained and immediate release of Aceclofenac.

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